current Medical Diagnosis & Treatment 1983

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From inability to let well alone; from too much zeal for the new and contempt for what is old; from putting knowledge before wisdom, Science before Art and cleverness before common sense; from treating patients as cases, from making the cure of the disease more grievous than the endurance of the same, Good Lord deliver us.

–Sir Robert Hutchison

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Preface

Current Medical Diagnosis & Treatment 1983 is intended to serve health practitioners as a useful desk reference on widely accepted methods currently available for diagnosis and treatment. It is not intended to be used as a textbook of medicine. Selected current references to the clinical literature and general bibliographies—emphasizing material published within the last 5 years—are included as a guide to further study.

The book has been revised annually since its first appearance in 1962, and its continued wide acceptance has been most gratifying. The widespread dissemination of this book overseas, both in translation and in its English language editions, has been a particular source of satisfaction to all of us who have worked on it over the years. A Spanish edition is available from El Manual Moderno (Mexico City), an Italian edition from Piccin Editore (Padua), a Serbo-Croatian edition from Savremena Administracija (Belgrade), a Portuguese edition from Atheneu Editora (São Paulo), a German edition from Springer-Verlag (Heidelberg), a Greek edition from Gregory Parisianos (Athens), and a Dutch edition from Kooyker (Leiden). A French translation is in preparation. An English edition for distribution in Asia is printed in Singapore by Maruzen, and a Middle East edition (in English) is available under the imprint of Librairie du Liban (Beirut). English editions are also produced in Taiwan, the Philippines, and Korea.

The editors wish to express their sincere thanks to their associate authors for participating so effectively in this venture, and to the many students and physicians who have contributed suggestions and criticisms for this and previous editions. We continue to solicit comments and recommendations for future editions.

Marcus A. Krupp
Milton J. Chatton

January, 1983

NOTICE

The authors and editors have been careful to recommend drug dosages that are in agreement with current official pharmacologic standards and the medical literature. Because all drugs may evoke idiosyncratic or toxic reactions, because drugs may interact with others in ways that modify therapeutic effectiveness and toxicity, and because some drugs are teratogenic, it is recommended that all clinicians review drug manufacturers' product information (eg, package inserts), especially in the case of new or infrequently prescribed medications. Furthermore, one must be thoroughly conversant with any drugs used in order to advise the patient about signs and symptoms of potential adverse reactions and incompatibilities.

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General Symptoms | 1

Milton J. Chatton, MD

PAIN

Pain in its myriad forms, including aching, soreness, and tenderness, is the most common symptom for which patients seek relief. Acute pain is an unpleasant experience primarily associated with tissue injury, and the protective response patients have to pain provides the clinician with critical diagnostic information. In taking a history from the patient with pain, there should be a careful elicitation of characteristics such as chronology, nature, location, radiation, and aggravating and alleviating factors that influence the pain. Because pain is a subjective phenomenon, it is not surprising that the description of pain by the patient may be difficult to interpret. Questioning should be as nearly suggestion-free as possible.

The reaction to pain, a function of the higher centers, is extremely variable and influenced by many factors depending upon the individual patient and the situation. When pain becomes chronic, the multifactorial influences (eg, anxiety; depression; social, cultural, and economic factors; and secondary gain) play an even larger role. It is therefore essential to determine, whenever possible, the primary cause (eg, infection), the pathogenesis (eg, inflammation, ulceration, anoxia), and the secondary or contributing factors.

The relief of pain is achieved by removal of the primary cause (eg, cure of infection), neutralization of the effect of the stimulus (eg, antacids for peptic ulcer), relief of discomfort (eg, rest, physiotherapy), suppression of the disease process (eg, anti-inflammatory drugs), and, when these are not feasible, by dulling or obliterating the sense of pain (eg, palliative narcotics for terminal cancer).

The hazards of administering analgesics without first attempting to establish a diagnosis cannot be overemphasized (eg, acute abdominal pain). Analgesics, particularly narcotics, may mask the symptoms of serious acute or chronic illness.

Pain may be treated nonspecifically with drugs (which may act at the receptor, spinal cord, or brain levels), physical measures (eg, heat, cold, immobilization), nerve block (eg, local anesthesia), surgery (eg, chordotomy), and by other measures of uncertain mechanism (eg, acupuncture). There is highly suggestive evidence that endogenous opioid peptides in the brain and pituitary—the endorphins—may be released by stress and other stimuli to produce analgesia. It is postulated that the release of these morphinelike endogenous brain chemicals is responsible for the absence of pain in some instances of extensive trauma and for the remarkable relief of pain provided by such divergent therapeutic measures as acupuncture, placebos, hypnosis, and electrical stimulation.

Because psychic or emotional factors may greatly influence the pain threshold, it is important to consider the "placebo" role of all therapeutic measures for the control of pain. Pharmacologically inactive drugs may be surprisingly effective in alleviating the pain of organic as well as functional disorders—hence the hazard in the use of the placebo for differentiation of organic from functional (psychologic) pain. Reassurance and explanation are thus important factors in relieving pain with or without analgesic drugs.

Current concern about the widespread use of addictive and abused drugs—and the inconvenience resulting from official restrictions placed upon their medicinal use—may sometimes lead to reluctance to prescribe narcotic analgesics when they are needed for pain relief. (See Schedule of Controlled Drugs, p 1087.) It must not be assumed that the average patient is addiction-prone. Although the various narcotics may have different addictive potentials, it is unreasonable to believe that addiction can be circumvented by substituting less effective but nonetheless addicting synthetic narcotic analgesics. Simply stated, it is a good rule to give the lowest effective dose of the appropriate agent for the given clinical circumstance to provide adequate symptomatic relief only as long as is necessary. Obviously, measures directed at correcting the cause of pain deserve first consideration. Remember that with the development of drug tolerance, narcotics have relatively little analgesic effect. It may be necessary to give the narcotic on a "once only" or "twice only" or interim basis. When pain is severe and intractable, however, as in terminal cancer, it is inhumane to permit unnecessary suffering. It does not suffice that the physician alone be aware of these general concepts or attitudes; they should be known to all other individuals (eg, nurses, relatives) who may be responsible for the administration of narcotic drugs to patients under the physician's care.

Chronic Pain (See also p 631.)

The relief of chronic pain can be one of the most perplexing and difficult problems encountered in medicine. The cause of chronic pain is often unknown or obscure, and although treatment aimed at known causes of pain is of primary importance, it is often necessary to resort to indirect and multidisciplinary therapeutic methods.

Acupuncture as a means of providing pain relief has been used in the Orient for centuries, but the method has not had widespread acceptance in the USA. The mechanism of acupuncture analgesia remains uncertain.

Hypnosis as a means of controlling chronic pain has a fluctuating history of acceptability and practice. Hypnosis may relieve sensory pain in some responsive patients through both tranquilizing and placebo effects. Numerous other psychologic techniques such as operant conditioning, biofeedback, progressive relaxation, distraction, and placebo have had varying degrees of success in relieving pain.

Transcutaneous electrical nerve stimulation is a simple and effective means of relieving well-localized chronic pain in some patients.

Neurosurgical procedures (eg, chordotomy, deep brain electrical stimulation), although generally considered as a last resort for chronic pain relief, should not be unnecessarily delayed to the point of hopeless invalidism and addiction.

Nonaddictive Analgesics

The systemic nonnarcotic analgesics act peripherally to block pain; their common mechanism of action is probably due to their common ability to inhibit prostaglandin synthesis.

A. Salicylates: The salicylate drugs are analgesic, anti-inflammatory, uricosuric, and antipyretic. They are useful in relieving myalgias, neuralgias, arthralgias, headaches, and dysmenorrhea. Untoward reactions are usually mild, consisting of dizziness and dyspepsia, but large doses may cause tinnitus, deafness, blurring of vision, nausea and vomiting, diarrhea, gastrointestinal hemorrhage, hepatitis, renal impairment, diaphoresis, headache, and delirium. In sensitive patients, salicylates may cause urticaria, asthma, and acute laryngeal edema.

1. Aspirin—Aspirin is available as plain, buffered, or enteric-coated 0.3-g tablets. The usual dose is 0.3–0.6 g with plenty of water every 4 hours as needed. Gastrointestinal irritation may sometimes be reduced by administration of the drug on a full stomach or with an antacid. The enteric-coated preparation is slower-acting, but it prevents gastric irritation and is also useful for patients who might be skeptical of the analgesic value of "ordinary aspirin." Some enteric-coated preparations, however, go through the gastrointestinal tract without being absorbed.

Aspirin can cause gastric irritation and increased microscopic blood loss from the gut in otherwise healthy individuals and is an occasional cause of massive gastrointestinal hemorrhage. It should not be used in patients with acute or chronic gastrointestinal problems—especially gastrointestinal bleeding—or active hepatic disease. The decision to withhold aspirin for other reasons from patients who might benefit from it must be made on an individual basis.

Hypersensitivity or intolerance to aspirin does occur, although uncommonly in view of the widespread use of the drug, and in rare instances the consequences may be very serious. Aspirin intolerance may be due to allergy but is more frequently due to an unexplained primary connective tissue disorder of the susceptible patient. Intolerance to aspirin often develops spontaneously in young or middle-aged adults who were formerly able to take aspirin without difficulty. Intolerance may be manifested by rhinorrhea, nasal polyposis, asthma, prolonged bleeding time, and anaphylactic shock. The possibility that such symptoms may be caused by aspirin must always be considered, since further use of the drug is contraindicated in intolerant patients. The incidence of true aspirin allergy (ie, with an immunochemical basis) is probably less than 0.1%, although it may be as high as 2–5% in known asthmatics.

Aspirin may interact adversely with the anticoagulant drugs and with phenylbutazone, probenecid, and spironolactone; patients who are taking these drugs should be advised against the use of aspirin in all forms.

Aspirin ingestion increases the bleeding tendency in patients with a wide variety of bleeding problems (eg, anticoagulant therapy, von Willebrand's disease). Because of temporary impairment of platelet function by aspirin, blood donors should avoid aspirin for 48–72 hours before giving blood.

2. Other salicylate preparations—Aspirin is widely employed in combination with caffeine or with caffeine and phenacetin (APC) for so-called synergistic effects. It is very doubtful if these combinations have any pharmacologically significant advantages over ordinary aspirin. The large amounts of phenacetin ingested by habitual users of some of these combinations may cause serious renal damage, although there is some doubt about the role of phenacetin itself as the cause of kidney injury.

Sodium salicylate, enteric-coated, 0.3–0.6 g every 4 hours, may be used by patients with gastric intolerance to aspirin. It is less effective than aspirin.

Salicylamide is a relatively weak, short-acting drug related to the salicylates that is found in numerous proprietary analgesic drug combinations. It is not hydrolyzed to salicylates in the body and so is excreted as the amide. It has doubtful advantages over aspirin or acetaminophen.

B. Acetaminophen: Acetaminophen in a dosage of 325–650 mg orally 3–4 times daily has an analgesic potency comparable to aspirin for many painful conditions. It has no anti-inflammatory actions and is therefore ineffective in rheumatoid arthritis and other inflammatory disorders. Its antipyretic action is comparable to that of aspirin. Acetaminophen may be especially useful as a mild analgesic and antipyretic

agent in aspirin allergy and in patients with gout. In therapeutic doses, the drug is relatively free of adverse side-effects. It apparently does not produce coagulation defects, does not cause gastric irritation and mucosal bleeding, and does not interfere with the tubular excretion of uric acid. Hypersensitivity reactions and hematologic abnormalities are quite rare. Simultaneous use of the drug with alcohol is inadvisable. Large doses of acetaminophen taken over a prolonged period may cause hepatotoxicity. Very large doses—taken accidentally or with suicidal intent—can cause liver damage or even fulminant hepatic failure.

C. Phenylbutazone and Oxyphenbutazone: Phenylbutazone and its metabolite or parahydroxy analog oxyphenbutazone exert a potent "analgesic" effect in painful disorders associated with inflammatory diseases. Although useful in a variety of acute rheumatic conditions, they are most effective in the treatment of acute gouty arthritis and active ankylosing spondylitis. Because of their relatively high potential for toxicity, they should be reserved for patients who do not respond to salicylates and other simple therapeutic measures. They should be used cautiously within the recommended dosage range, usually 300–400 mg/d (or less), in divided doses. The manufacturer's directions should be followed carefully. If, after a trial period of 1 week, the drugs fail to produce a favorable response, therapy should be discontinued. Toxic reactions include skin rash, hypersensitivity reactions of the serum sickness type, nausea and vomiting, stomatitis, peptic ulceration, sodium retention, blood dyscrasias, and prothrombin depression (when the drugs are used concurrently with anticoagulants of the coumarin type). As a precaution, blood counts are recommended twice weekly for the first month, weekly for the second month, and monthly thereafter. In general, the drugs should not be used in patients with gastrointestinal, renal, cardiac, or hematopoietic disease or in those receiving anticoagulant therapy. They should not be given for prolonged periods, and all patients should be observed frequently for evidence of toxicity.

D. Indomethacin: This analgesic and anti-inflammatory agent is said to be useful in the rheumatic disorders, although its advantages over aspirin, if any, remain controversial. Indomethacin should not be used as a "routine" mild analgesic (eg, instead of aspirin). It appears to be most effective in ankylosing spondylitis and in osteoarthritis of the hip. The usual dose is 25 mg 2–4 times daily, increasing the dosage, if tolerated, up to no more than 200 mg daily. Untoward effects include headache, dizziness, light-headedness, tinnitus, psychiatric disturbances (including depression and psychosis), drug rash, stomatitis, anorexia, dyspepsia, nausea and vomiting, peptic ulceration, gastrointestinal bleeding, diarrhea, and renal insufficiency. Because visual disturbances may occur (corneal deposits, retinopathy), periodic ophthalmologic evaluation is recommended. Psychiatric disorders, epilepsy, and parkinsonism may be aggravated by the drug. Hematologic or hepatotoxic effects are relatively uncommon. Because of the side-effects and toxicity, patients receiving indomethacin should be observed carefully for any evidence of toxicity.

E. Newer Anti-inflammatory Analgesics: Several newer antipyretic, anti-inflammatory analgesic drugs are available largely for the treatment of rheumatoid arthritis and certain other arthritic disorders in patients who are intolerant of aspirin. These compounds appear to cause fewer adverse reactions than aspirin when the latter is given in the usual anti-inflammatory doses. Gastric irritation seems to be less than with aspirin, but the drugs should still be used cautiously in patients with a history of peptic ulcer; severe gastrointestinal bleeding reportedly due to the drugs completely precludes their use in patients known to have active peptic ulcers. The drugs, like aspirin, can interfere with blood coagulation and may cause bleeding in patients with a hemorrhagic diathesis.

These agents should not be used concomitantly with aspirin or in patients with a history of nasal polyps, rhinitis, urticaria, or bronchospasm associated with aspirin use. They should not be taken during pregnancy and lactation.

Side-effects may include gastrointestinal disturbances, skin rashes, headaches, dizziness, drowsiness, visual disturbances, tinnitus, palpitation, dyspnea, and sodium retention. There have been increasingly frequent case reports of renal impairment with many of the newer agents.

The recommended dosages are as follows:

Fenoprofen (Nalfon), 300–600 mg orally 4 times daily.

Ibuprofen (Brufen, Motrin), 300–400 mg orally 3–4 times daily.

Meclofenamate sodium (Meclomen), 100 mg 3 times daily.

Naproxen (Naprosyn), 250 mg orally twice daily.

Piroxicam (Feldene), 20 mg orally once daily.

Sulindac (Clinoril), 200 mg orally twice daily.

Tolmetin (Tolectin), 400 mg orally 3 times daily.

Zomepirac (Zomax), 100 mg 4 times daily.

F. Carbamazepine (Tegretol): This tricyclic compound, which is chemically related to imipramine, is remarkably effective in relieving pain in about 75% of patients who have had trigeminal neuralgia for long periods and in some cases has induced prolonged remissions (see p 599). Pain relief may occur within 48 hours. Periodic attempts should be made to withdraw the drug to determine if the patient has had a spontaneous remission; the drug is resumed if the pain recurs. Carbamazepine has also been used unpredictably and less effectively in other severe neuralgias, in pain due to tabes dorsalis, and in trigeminal neuralgia occurring as a manifestation of multiple sclerosis. Some patients who do not respond to carbamazepine require the addition of phenytoin or surgical treatment.

Moderately or Potentially Addictive Analgesics

A. Codeine: Codeine is pharmacologically simi-

lar to morphine but is less potent. Codeine diminishes the cough reflex and decreases bowel motility (constipating). It is preferred to morphine for relief of moderate degrees of pain because it is much less habit-forming and causes fewer untoward reactions (urticaria, nausea and vomiting, pruritus, dermatitis, anaphylactoid reactions).

1. Codeine phosphate, 8–65 mg orally or subcutaneously every 3–4 hours as needed. If 65 mg is ineffective, stronger narcotics should be used rather than larger doses of codeine, which only cause more severe side-effects without enhanced analgesic effect.

2. Codeine in dosages ranging from 8 to 65 mg is often used in combination with aspirin or ASA compound to produce an additive analgesic effect. The dosage is 1 tablet orally 3–4 times daily as necessary.

B. Propoxyphene: Propoxyphene (Darvon), given in doses of 30–65 mg orally every 6 hours as needed, although related chemically to the narcotics, is considerably less potent in all respects. Addiction may occur nevertheless. In the USA, propoxyphene was recently classified as a schedule III controlled drug. Side-effects are uncommon (dizziness, epigastric pain, nausea, jaundice). Neonatal drug withdrawal reactions may be associated with maternal use. The analgesic potency is about the same as that of aspirin. Its principal use is in patients who are allergic to or who cannot tolerate aspirin or codeine. Many cases of suicide with propoxyphene have been reported.

C. Agonist-Antagonist Opioids: The agonist-antagonist opioids have both morphinelike and narcotic antagonist properties. Although these drugs approach the analgesic effectiveness of morphine, special anticipated benefits have not yet been completely realized. For example, when pentazocine is administered orally, its effectiveness only approximates that of codeine. Nalbuphine is being investigated as a preferred analgesic in acute myocardial infarction because it is relatively free from clinically important deleterious effects on cardiac pump function.

Tolerance develops more slowly to agonist-antagonist analgesics than to morphine. Although dependence liability is less than with conventional narcotics, caution should be exercised with addiction-prone individuals; the drugs can induce withdrawal symptoms in narcotics addicts. Sedation is a common side-effect; dizziness, nausea, and vomiting can occur. Especially with pentazocine, psychotomimetic reactions may occur, and skin ulceration and fibrous myopathy at injection sites are not uncommon after long-term use.

The dosages are as follows: butorphanol (Stadol), 1–2 mg intramuscularly or intravenously every 4 hours as needed; nalbuphine (Nubain), 10 mg intramuscularly or intravenously every 3–6 hours as needed; pentazocine (Talwin), 50–100 mg orally, or 30 mg intramuscularly, intravenously, or subcutaneously, every 3–4 hours as needed.

Strongly Addictive Analgesics

The strongly addictive narcotic analgesics alter the perception of pain by their effects on the central nervous system. They are indicated for the relief of pain that is too intense to be controlled with nonnarcotic drugs or when pain is of a type not relieved by the salicylates (eg, visceral pain).

The narcotics are also mildly sedative in small doses; larger doses produce sleep, stupor, and respiratory depression. They are addictive and should be used cautiously and with careful attention to federal and state laws. Except for codeine, the narcotics should not be used for chronic illnesses unless necessary for the control of intractable pain in terminal illness.

Addiction and withdrawal and the specific treatment of intoxication with these drugs are discussed in Chapter 17.

Note: Always use the least potent narcotic drug that will control the pain, eg, codeine is preferable to meperidine, and meperidine is preferable to morphine.

A. Morphine: This drug is the most valuable of the potent narcotics for general clinical use. It causes central nervous system depression that results in powerful analgesia associated with sedation, euphoria, and hypnosis; selective respiratory center depression; and dulling or abolition of the cough reflex. It increases intracranial pressure. Morphine is useful for the relief of acute severe pain. It is the drug of choice for the pain of myocardial infarction and is also valuable in the treatment of severe cardiac dyspnea (eg, pulmonary edema or cardiac asthma of left ventricular failure). It is a valuable preoperative drug. Morphine is contraindicated in morphine sensitivity, bronchial asthma, undiagnosed surgical abdominal disease, hepatic insufficiency, hypothyroidism, morphinism, head injury, Addison's disease, and whenever the possibility of vomiting may be dangerous. The hypnotic effect associated with the analgesia produced by morphine may be undesirable. Untoward reactions include respiratory depression, shock, nausea and vomiting, severe constipation, urticaria, and pruritus. The addiction tendency is great, especially in addiction-prone individuals.

1. Morphine sulfate, 8–15 mg orally or subcutaneously. In cases of severe agonizing pain—especially pain associated with impending neurogenic shock—morphine may be given slowly intravenously in 5 mL of physiologic saline. It is probable that only increased duration of effect is gained by increasing the dose above 10 mg.

2. Morphine adjuncts–Belladonna alkaloids such as atropine and scopolamine, 0.3–0.6 mg subcutaneously along with morphine, may reduce some of the untoward effects of morphine. The phenothiazine tranquilizers may enhance the sedative effect of morphine, making it possible to give the latter in smaller doses.

Brompton mixture, an elixir containing morphine and cocaine, is used for the relief of chronic pain in inoperable cancer. It should be given on an individualized regular schedule with a phenothiazine in ap-

propriate dosage to prevent pain while preserving a normal sensorium.

B. Morphine Congeners: The drugs in this category are equivalent to morphine but have no appreciable advantages. The following subcutaneous doses are equivalent to 10 mg of morphine: hydromorphone (Dilaudid), 2 mg; levorphanol (Levo-Dromoran), 2 mg; oxymorphone (Numorphan), 1 mg.

C. Methadone: Methadone has powerful addictive properties. The only situation in which methadone is preferred is in the authorized treatment of narcotic addiction; withdrawal symptoms are ameliorated if methadone is first substituted for heroin or other opiates (see Chapter 17). Methadone, 2.5–10 mg subcutaneously or intramuscularly, is also used as a morphinelike analgesic. Given orally, the drug is only one-half as effective as morphine, its onset is slower, and its effect is more prolonged.

D. Meperidine (Demerol): 75–150 mg orally or intramuscularly (not subcutaneously) every 3–4 hours provides analgesia and causes less intense side-effects than morphine. It is less addictive than morphine, but addiction to meperidine is very common nonetheless.

E. Meperidine Congeners: Alphaprodine, 60 mg subcutaneously, and anileridine, 50 mg subcutaneously, are equivalent to meperidine, 100 mg, except that their duration of action is shorter.

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FEVER & HYPERTHERMIA

Fever was well known to the ancients as an important manifestation of illness, but it remained for modern medical science to provide a better understanding of the significance of body temperature variations in health and disease. As the large number of specific causes of fever were being identified over the past century, interest also turned toward the pathogenesis of fever. It is now believed that fever, or pyrexia, represents regulation of body temperature at an elevated thermoregulatory "set point" (ie, to a new point above 37 °C). The thermoregulatory center is in the hypothalamus. When bacterial toxins or other stimuli act on the body's bone marrow–derived phagocytic cells (eg, leukocytes), they produce endogenous pyrogens that circulate to the thermoregulatory center and cause an elevation of the set point. The temperature elevation may result from either increased heat production (eg, shivering) or decreased heat loss (eg, peripheral vasoconstriction).

Hyperthermia, usually an exogenous process, differs from fever in that it occurs when the body temperature is higher than the thermoregulatory set point. It occurs when body metabolic heat production or environmental heat load exceeds normal heat loss capacity or when there is impaired heat loss.

The body temperature is normally subject to individual variation as well as to fluctuation due to physiologic factors, eg, exercise, digestion, sudden increase in environmental temperature, and excitement. The normal diurnal variation may be as much as 1 °C, being lowest in the early morning and highest in the late afternoon. There is a slight sustained temperature rise following ovulation during the menstrual cycle and in the first trimester of pregnancy.

The average normal oral body temperature is 37 °C (range 36–37.4 °C), or 98.6 °F (range 96.8–99.3 °F). The normal rectal or vaginal temperature is 0.5 °C (1 °F) higher than the oral temperature, and the normal axillary temperature is correspondingly lower.

While fever as a symptom should generally be regarded with appropriate concern, in some circumstances it may play a beneficial role. Experimental evidence and clinical observation suggest that host defense response may be enhanced in the presence of fever, and, conversely, inability of a patient to produce fever may carry a grave prognosis. In the preantibiotic era, fever was employed with limited success as nonspecific therapy for chronic infections. Hyperthermia was used with limited success in treatment of certain neoplastic diseases. Markedly elevated or prolonged fevers may result in profound metabolic disturbances. High fever during the first trimester of pregnancy may cause birth defects that are apparently unrelated to the

cause or treatment of the fever. Fever per se may increase insulin requirements and also alter the metabolism and disposition of drugs used for the treatment of the diverse diseases associated with fever. Prolonged elevation of rectal temperature over 41 °C (105.8 °F) may result in permanent brain damage; when the rectal temperature is over 43 °C (109.4 °F), heat stroke occurs and death is common.

The body temperature may provide important information about the presence of illness and about changes in the clinical status of the patient. The fever pattern (graphic record), however, is of rather limited use for specific diagnosis. Furthermore, the degree of temperature elevation does not necessarily correspond to the severity of the illness. In general, the febrile response tends to be greater in children than in adults; in elderly persons, the febrile response is less marked than in younger adults. A sudden fall in temperature in the febrile patient is not necessarily a favorable sign; unless there is a corresponding improvement in the patient's well-being, it may portend a serious complication such as shock.

Diagnostic Considerations

The outline below illustrates the wide variety of clinical disorders that may cause fever. Most febrile illnesses are due to common infections, are short-lived, and are relatively easy to diagnose. In certain instances, however, the origin of the fever may remain obscure ("fever of undetermined origin," FUO) after careful diagnostic examination. Meticulous history taking (including history of exposure to infection, travel, drugs), careful physical examination, extensive laboratory and x-ray studies, and even exploratory surgical procedures may be required (see Chapter 21).

In about 40% of cases, the cause of FUO is infectious disease. About 20% of cases of FUO are due to neoplastic disease; about 15% are due to connective tissue disease; and the remainder are due to miscellaneous causes. In 5–10% of cases, the diagnosis is never established.

Use of the so-called therapeutic test for the diagnosis of a febrile disorder is justified only when a specific disease is strongly suspected and when a diagnosis cannot be established by other means (eg, chloroquine for malaria). Hasty, empiric use of polypharmaceutic measures (eg, multiple antimicrobials, corticosteroids, antipyretics, analgesics) may seriously interfere with rational diagnosis and therapy and may actually be hazardous. The possibility of factitious or self-induced fever should be considered in patients with underlying psychiatric disorders.

Clinical Classification of Causes of Fever (With Examples)

(1) Infections: Viral, rickettsial, bacterial, fungal, and parasitic infections are the commonest causes of fever. (a) Generalized infections without localizing signs (eg, septicemia). (b) Generalized infections with localizing signs (eg, scarlet fever). (c) Localized infections (eg, pyelonephritis).

(2) Collagen diseases: Systemic lupus erythematosus, polyarteritis nodosa, dermatomyositis, rheumatoid arthritis, rheumatic fever.

(3) Central nervous system disease: Cerebral hemorrhage, head injuries, brain and spinal cord tumors, degenerative central nervous system disease (eg, multiple sclerosis), spinal cord injuries.

(4) Malignant neoplastic disease: Primary neoplasms (eg, of thyroid, lung, liver, pancreas, and genitourinary tract). Secondary neoplasms, carcinoid.

(5) Hematologic disease: Lymphomas, leukemias, pernicious anemia, hemolytic anemias, hemorrhagic disease (eg, hemophilia).

(6) Cardiovascular disease: Myocardial infarction, thromboembolic diseases, infective endocarditis, pulmonary embolism, paroxysmal tachycardias.

(7) Gastrointestinal disease: Inflammatory bowel disease, cirrhosis (necrotic phase), liver abscess.

(8) Endocrine disease: Hyperthyroidism, pheochromocytoma.

Table 1–1. Pathophysiology, clinical findings, and treatment of fever and hyperthermia.*

Pathophysiologic Basis for Fever	Clinical Findings	Treatment
Endogenous pyrogens act on hypothalamus to induce fever (eg, infection, collagen disease, allergy).	Patient complains of feeling cold. Shivering. "Gooseflesh."	Antipyretic drugs: aspirin or acetaminophen, 300–600 mg 4 times daily. Supply clothing and covers just sufficient for maximal comfort. *Avoid* measures for physical removal of heat (eg, sponging, ice bags).
Agent or illness acts on hypothalamus to induce fever (eg, central nervous system lesions, toxins, radiation).	Cold extremities. Minimal sweating.	
Heat production exceeds normal heat loss mechanisms (eg, malignant hyperthermia, thyroid storm).	Patient complains of feeling hot. Hot extremities. Active sweating (except in cases where there is defective heat loss mechanism).	Remove excessive clothing or covers. Eliminate excess environmental heat source. Employ measures for physical removal of heat (eg, sponging, ice bags, ice-water enemas). *Avoid* antipyretic drugs.
Environmental heat load exceeds normal heat loss mechanisms (eg, exposure to industrial heat, overuse of sauna).		
Defective heat loss mechanisms cannot cope with normal heat load (eg, heat stroke, burns, sweat gland disorders).		

*Modified and reproduced, with permission, from Stern RC: Pathophysiologic basis for symptomatic treatment of fever. *Pediatrics* 1977;59:92.

(9) Diseases due to physical agents: Heat stroke, radiation sickness, trauma (eg, surgery).

(10) Diseases due to chemical agents: Drug reactions, anesthesia (malignant hyperpyrexia), anaphylactic reactions, serum sickness, chemical poisoning, pyrogen reactions (following intravenous fluids).

(11) Disorders of fluid balance: Dehydration, acidosis.

(12) Other miscellaneous diseases: Sarcoidosis, amyloidosis.

(13) Psychogenic fever.

(14) Factitious, or "false," fever.

(15) Unknown causes.

Treatment

A. Removal of the Specific Cause of the Fever: The principal problem is to determine and eradicate the cause of the fever. Symptomatic measures directed solely toward depression of elevated body temperature are not indicated except for high, prolonged fevers.

Prevention of the serious "malignant hyperpyrexia" that may follow certain types of anesthesia (succinylcholine and potent inhalation anesthetics) can best be accomplished by recognizing the patient who is predisposed by virtue of heredity (past personal or family history of difficult anesthesia) and by choosing the proper anesthetic agent, with temperature monitoring during the entire course of anesthesia. As soon as the syndrome is detected, emergency treatment is required. Prompt and vigorous body cooling (see below), hyperventilation with 100% oxygen, intravenous dantrolene, and measures to correct metabolic acidosis and renal failure are instituted.

B. Reduction of Fever by Nonspecific Means: When the body temperature is greater than 40 °C (104 °F), particularly if prolonged, symptomatic treatment may be required (Table 1–1). Since moderately high fevers are usually well tolerated by the body, with little direct tissue damage, aggressive symptomatic treatment should be avoided. *Extreme pyrexia (hyperpyrexia) — temperatures in excess of 41 °C (105.8 °F) — is a medical emergency!* (See Heat Stroke, p 960.)

1. Measures for removal of heat–Alcohol sponges, cold sponges, ice bags, and ice-water enemas will reduce fever and provide physical comfort for patients who complain of feeling *hot*. Use of these measures should be appropriate to the degree of fever and discomfort and is to be avoided when the febrile patient feels and looks *cold*.

2. Antipyretic drugs–Aspirin or acetaminophen, 0.3–0.6 g every 4 hours as needed, is quite effective in reducing fever due to diseases that act upon the hypothalamic thermoregulatory center. The drugs may occasionally obscure the clinical picture and cause undesirable side-effects such as excessive sweating, nausea and vomiting, skin eruptions, and hematologic changes (see p 2).

3. Fluid replacement–Oral or parenteral fluids must be administered in amounts sufficient to compensate for the extra fluid and electrolyte losses from perspiration and all other causes.

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WEIGHT LOSS

Marked weight loss is often an indication of serious physical or psychologic illness. If the weight loss is immediately discernable from the patient's physical appearance, the clinician should proceed promptly with appropriate (but not necessarily exhaustive) diagnostic studies based upon the findings of a careful history, physical examination, and routine laboratory studies.

Weight loss may be due to a wide variety of acute and chronic disease processes (eg, malignancy, infection, toxins) of any organ system of the body, as well as to psychiatric disorders. If the initial evaluation is done with discernment, many of the physical causes of weight loss can be relatively quickly uncovered. It is important early to correlate weight change with a history of significant change in appetite, physical activity, and psychosocial factors.

When the patient complains of weight loss but appears to be adequately nourished, inquiry should be made about exact weight changes (with approximate dates) and about changes in clothing size. Family members may provide confirmation of weight loss.

Once it has been established that the patient has marked weight loss, further methodical laboratory and radiologic investigation may be indicated. For unexplained reasons, marked weight loss can sometimes occur in the absence of serious physical illness. Psychiatric consultation should be considered when there is evidence of depression, anorexia nervosa (see p 793), or other psychologic problems.

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FATIGUE

Fatigue and the closely related complaint of weakness are most often readily explained by apparent common factors such as overexertion, poor physical conditioning, inadequate rest, marked obesity, inadequate nutrition, and emotional problems. The possibility that excessive fatigue may be due to physical

illness, particularly in its incipient phase, sometimes makes it necessary to search for a wide variety of organic causes (see below).

A carefully elicited history of the patient's daily living habits and working environment may obviate the need for extensive and unproductive medical studies. The presence of fatigue on arising in the morning and a history of emotional stress or of recurrent episodes of anxiety or depression lend support to a functional diagnosis.

Some of the organic causes of fatigue that might be considered are the following:

(1) Endocrine disorders: Addison's disease, hypothyroidism, hyperthyroidism, diabetes mellitus.

(2) Neurologic disorders: Myasthenia gravis.

(3) Infectious disease: Hepatitis, tuberculosis, brucellosis, infective endocarditis, intestinal parasites.

(4) Respiratory disorders: Emphysema, asthma.

(5) Hematologic disorders: Anemia, infectious mononucleosis.

(6) Collagen disorders: Rheumatoid arthritis, systemic lupus erythematosus.

(7) Malignancies: Any type.

(8) Drugs and toxins: Alcohol, sedatives and tranquilizers, environmental toxins.

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SHOCK SYNDROME (Circulatory Shock)

"Shock" is a complex group of acute cardiovascular syndromes that defy precise definition because of their varied origins. It is practical, however, to consider shock as a disturbance of circulation resulting in ineffective or critical reduction of perfusion of vital tissues with hypoxia and a wide range of systemic effects. The term is descriptive of a "classic" but highly variable pattern of signs and symptoms that usually includes arterial hypotension, altered sensorium, ashen pallor, clammy skin, rapid and weak pulse, air hunger, thirst, oliguria, and a tendency to steadily progress toward a refractory and so-called irreversible phase. Recognition of early shock may be obscured by factors such as anxiety, complicating medical problems, and surrounding circumstances. The "classic" signs of shock may appear suddenly and often represent fully developed shock.

In so-called warm shock such as may be seen in the early phase of septic shock, the skin is pink and warm, and the urine volume is adequate despite the arterial hypotension and peripheral pooling.

The 3 major pathophysiologic mechanisms involved in the production of shock are (1) hypovolemia (decreased effective blood volume), (2) cardiac insufficiency (pump failure), and (3) altered vascular resistance (vasoconstriction or vasodilatation).

Alteration of one or more of these factors may result in diminished microcirculatory flow. It is the adaptation or failure of adaptation of the microcirculation that is responsible for arteriovenous shunting, decreased urine output, fluid loss from the capillaries, sludging of red blood cells, disseminated intravascular coagulation, stagnant tissue hypoxia, acidosis, hyperlacticacidemia, and cellular injury, all of which occur in the shock syndrome.

Debility, malnutrition, senility, temperature extremes, alcoholism, hypotensive drugs, anesthetics, autonomic disorders, diabetes, and adrenocortical disorders are factors that can predispose to shock. Acute alcoholism may cause a misleading and unexplainable severe hypotension of several hours' duration without other evidence of clinical shock (ie, organ ischemia) in trauma patients. A rapid and thorough search for cause is essential.

Factors that unfavorably influence the prognosis in shock states include coma, acidosis ($pH < 7.30$), $P_{aCO_2} > 45$ mm Hg, serum lactate > 2 mmol/L, severe sepsis, anuria, heart disease, hepatic disease, and advanced age (> 70 years).

Classification

No classification of shock is completely satisfactory, but one that is based upon the predominant hemodynamic changes in the various types of shock is clinically the most useful (Table 1–2). It should be apparent that in a given patient with shock, several hemodynamic mechanisms are at work simultaneously, so that continuous monitoring of multiple parameters of cardiovascular function is required. For example, hypovolemia and altered peripheral resistance may be significant factors in cardiogenic shock, and pump failure may be an important feature of hypovolemic shock. Therapeutically, this implies a real

Table 1–2. Classification of shock.

I. Hypovolemic shock (decreased effective blood volume)
A. Exogenous (external) loss of fluid
1. Whole blood (eg, hemorrhage)
2. Plasma (eg, burns)
3. Fluid and electrolytes (eg, vomiting, diarrhea)
B. Endogenous (internal) loss of fluid
1. Exudative (eg, peritonitis)
2. Traumatic (eg, hematoma)
II. Cardiogenic shock (pump failure)
A. Intrinsic myocardial disorders (eg, decreased myocardial contractility)
1. Focal damage (eg, myocardial infarction)
2. Generalized disorder (eg, dysrhythmia, myocarditis)
B. Extrinsic disorders
1. Cardiac tamponade (eg, pericardial disease)
2. Obstruction of major blood channels (eg, pulmonary embolism)
III. Vascular (vasomotor, distributive, low-resistance) shock (altered vascular resistance and capacity)
A. Increased venous capacitance (pooling) (eg, bacterial endotoxin)
B. Decreased arteriolar resistance (eg, fright, pain, vasodilative drugs)